study, because all patients were screened for run-in phases 1 and 2. The patients with a low adherence rate might be excluded during run-in periods. Therefore, this excellent medication adherence rate observed in the present study might not be applicable to general Japanese hypertensive patients. In addition, many participants were not newly diagnosed hypertensive patients, but rather had been treated with antihypertensive drugs for several years.[25] Furthermore, a recent study demonstrated that merely participating in a clinical trial significantly increases adherence.[26] Even considering these limitations, however, the findings of the present study are largely new and provide important information on medication adherence regarding a combination pill of antihypertensive drugs.

Medication adherence is defined as the percentage of prescribed doses taken per a defined period of time. Various methods to evaluate medication adherence have been proposed. These methods are generally classified into 3 categories: subjective (eg, patients interview), direct (eg, measurement of drug concentrations in the blood), and indirect (eg, pill counts, prescription refills, electronic monitoring of medication use).[19] Although subjective methods are simple to conduct, this method might often be inaccurate. Electronic monitoring seems to be the most accurate method to evaluate medication adherence.[27] Unfortunately, however, the cost of this device precluded its use in the present study. Accordingly, the indirect method of pill counts was applied in the present study. This method can be applied to estimate the quantities of medications a patient presumably takes.

In conclusion, the present study has evaluated the impact of a combination pill of antihypertensive drugs on patients' medication adherence in a randomized controlled trial. The results showed no appreciable effects of a combination pill of antihypertensive drugs on medication adherence or blood pressure in Japanese hypertensive subjects over 6 months. The medication adherence rate was extremely high, which might be attributable to selection bias. Despite these results, a combination pill might be useful for the treatment of hypertension, because it would be convenient for patients to use a single pill for their treatment. Moreover, in view of the associations of the combination pills with medication adherence and blood pressure control demonstrated by previous observational studies, investigators should continue to study the potentially beneficial effects of combination pills, possibly together with other strategies to improve compliance, for longer treatment periods.

Disclosures

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Appendix

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Supplemental Files

Supplemental File 1

Table S1. Effects of Combination Pills on Adherence Rate

Figure S1. Mean systolic and diastolic blood pressures during run-in phases and after randomization.

Please find supplemental file(s);
http://dx.doi.org/10.1253/circj.CJ-11-1481

降圧薬合剤の患者満足度に関するアンケート調査：COMFORT 試験

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はじめに

高血圧は心血管疾患の重要な危険因子の一つであり，心血管疾患の発症を予防する上で厳格な降圧治療の必要性が，高血圧治療ガイドライン2009(JSH2009)においても強調されている[1]。降圧目標を達成するために降圧薬の併用療法が行われているが，ガイドラインが提唱する降圧目標に未達成の例も多いことが指摘されている[2]。良好な服薬アドヒアランスを維持した上で，適切な降圧薬の併用療法を実施することが治療の基本であるが，服薬薬剤数を増やして血圧をコントロールしようとした場合，患者の了解が得られにくいことを経験することもある。我が国においても降圧薬の合剤が日常臨床に広く使用されるようになり，服薬アドヒアランスに対する効果を検討するCOMFORT (Combination Pill of Losartan Potassium and Hydrochlorothiazide for Improvement of Medication Compliance Trial) 試験を多施設共同研究として実施した[3]。本試験の主結果では，服薬アドヒアランスと血圧コントロールには，合剤群と対照群とでは差を認めなかった[3]。しかし，合剤を用いた高血圧治療における患者の満足度を検討した報告は，これまでほとんど実施されていない。そこで，今回，COMFORT試験に参加した患者を対象として，降圧薬合剤を使用した場合の患者満足度のアンケート調査を実施した。高血圧治療における降圧薬合剤の位置づけを考える上で有用かと考えられるため，以下に報告する。

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Ⅰ．方法

COMFORT試験は，多施設共同，非盲検無作為化比較試験である。未治療あるいは治療中の高血圧患者でアンジオテンシン受容体拮抗薬（ARB）とサイアザイド系(類似薬を含む)利尿薬の併用療法を行うことができる者207名を合剤治療群（ロサルタンカリウム50mg/ヒドロクロロチアジド12.5mg）と対照群（ARB［ロサルタンカリウム50mg相当量］と利尿薬［ヒドロクロロチアジド6.25～12.5mg相当量］による併用療法）に無作為に割り付けて，合剤治療の服薬遵守および血圧コントロールに及ぼす影響を6ヵ月間にわたり観察した[3]。主結果は既に論文として発表している。本研究では，COMFORT試験の合剤治療群を対象として，追跡終了時における合剤を用いた治療の印象をアンケート調査した。

無作為割り付けの結果，103名が合剤治療群に割り付けられ，ARBとサイアザイド系利尿薬の併用治療から合剤治療（ロサルタンカリウム50mg/ヒドロクロロチアジド12.5mg）に変更された。これらの対象者のうち，追跡終了時にアンケート調査に回答があった86名を本研究の解析対象とし，アンケート未回答の17名は解析の対象からは除外した。調査（質問）項目は以下の通りである。

(1) 合剤を6ヵ月間服用し続けることができましたか？
(2) 以前服用していた薬と合剤はどちらがよいですか？
(3)「合剤がよい」と答えられた理由は？
(4)「以前服用していた薬がよい」と答えられた理由は？

質問(3)と(4)に関しては，複数の回答も可とした。

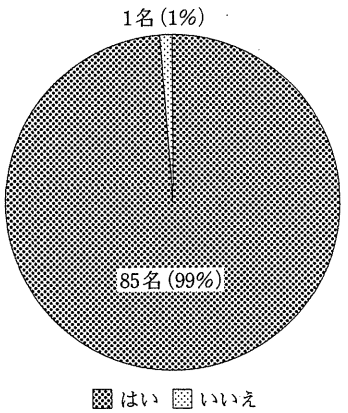

図 1　合剤服用継続の可否（質問1）

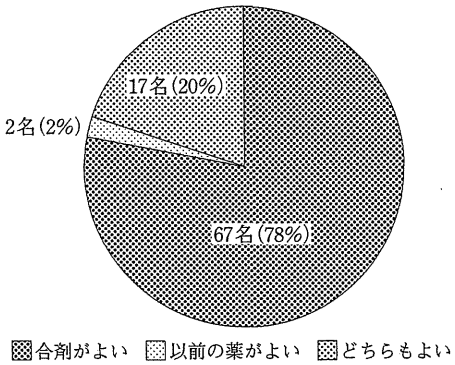

図 2　合剤と以前の薬とのどちらがよいか？（質問2）

Ⅱ．結　　果

図1に質問(1)の結果を示す。アンケートの回答を得ることが可能であった86名では1名が有害事象（消化管出血）のため服薬継続ができなかったが，他の85名は合剤服用継続が可能であったとの回答であった。なお，軽度な有害事象のため試験が中止された例が3例あったが，アンケートは回収できていない。既に報告している様に，有害事象に関しては合剤群と対照群とでは差はなく[3]，今回のアンケート結果をみても，合剤の忍容性は高いと考えられた。

次に，図2に質問(2)の結果を示す。「合剤がよい」との回答が67名（78%），「以前の薬がよい」との回答が2名（2%），「どちらもよい」との回答が17名（20%）であった。約4分の3の患者が新たに投与された合剤の方を好んでおり，降圧治療を行う上で合剤使用は有用であると考えられた。更に，質問(3)および(4)で，それぞれの理由を尋ねたところ，「薬の錠数が減った」と回答した者が70%，「血圧が以前より下がった」と回答した者が37%あり，合剤が好まれる主な理由は，この二点であると考えられた。一方，以前の薬がよいと回答した2名は，「血圧が十分に下がらなかった」ことを理由としてあげていた（表1）。

表 1　合剤あるいは以前の薬がよい理由

合剤がよい理由（67名）	
薬の錠数が減った	47名（ 70%）
血圧が以前より下がった	25名（ 37%）
副作用が減った	2名（ 3%）
その他	1名（ 1%）
以前の薬がよい理由（2名）	
血圧が十分に下がらなかった	2名（100%）

Ⅲ．考　　察

我が国においても，ARBとサイアザイド系利尿薬あるいはARBとカルシウム拮抗薬の降圧薬合剤が臨床の場で広く使用されている。服薬薬剤錠数が減ることに基づく服薬アドヒアランスの改善が合剤使用のメリットとして最も期待されているが，必ずしもきちんと証明はされていない。観察研究も解析対象として含めたメタ解析では，合剤治療により服薬率が上昇したとの報告もあるが[4]，我々が実施したCOMFORT試験では，対照群と合剤群とでは服薬率に差を認めなかった[3]。少なくとも日本人においては，明らかな差を簡単に認めるほどには，合剤治療により服薬アドヒアランスの改善は期待できないのではないかと考えられた。この点に関しては，更なる検討が必要と考えられ，長期間にわたる多数例を対象とした臨床試験が，今後実施されることを期待したい。

一方，今回のアンケート調査は，ARBとサイアザイド系（類似薬を含む）利尿薬の併用から合剤に変更した場合の主観的感想（満足度）を検討したものである。アンケート未回答の例がかなり含まれており，バイアスがあるものの，概して合剤を使用した場合の満足度が高いことを示している結果と考えられた。しかも，その主たる理由が，「薬の錠数が減った」ことと「血圧が以前より下がった」ことであった。服薬薬剤錠数の減少は降圧治療における患者の満足度に対して，大きな影響を及ぼす要因になると考えられた。

同様の結果は，いくつかの他の調査でも認められている。「新たな降圧薬追加に対する抵抗感」に関する調査では，約7割から8割の高血圧患者

が，何らかの抵抗感があると回答しており[5)6)]，医師が降圧目標達成のために降圧薬を増量する際の妨げになっている可能性があると考えられた。一方，診療所でカンデサルタンとアムロジピンの併用から合剤に変更した場合の調査においても，「経済的に助かる」「錠数が減るので便利」との理由で合剤の継続処方を希望する例が多く，「飲み忘れが減る可能性」を理由としてあげた患者は少数例にとどまったと報告されている[7)]。これらの調査結果は，本研究結果を支持するものであり，服薬薬剤錠数の問題は，高血圧治療を考える上で避けては通れない問題であると考えられた。

高血圧治療は長期に及ぶため，患者が納得して治療を受ける必要がある。また，心血管疾患の発症を予防するためには，ガイドラインで示しているように厳格な降圧治療を行わなければならない。これらのことを鑑みると，患者にとって満足度が高い治療を継続して実施することが，心血管疾患発症を予防する上で必須となってくると考えられる。合剤を用いた降圧治療は，これらの観点からも，有用な治療戦略の一つになると思われる。

おわりに

高血圧患者に対して，ARBとサイアザイド系（類似薬を含む）利尿薬の併用治療を合剤治療に変更した場合の患者満足度をアンケート調査にて評価した。合剤を用いた治療に対する患者の満足度は高く，その主たる理由は，服薬薬剤錠数の減少に基づくものであった。服薬薬剤錠数を考慮した上での降圧治療の実践が，厳格な降圧目標を達成する上でも重要になってくるのではないかと考えられた。

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COMFORT試験グループ

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文　献

1) 日本高血圧学会高血圧治療ガイドライン作成委員会：高血圧治療ガイドライン2009．日本高血圧学会．
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ARTICLES

大分大学医学部附属先端分子イメージングセンターにおけるPET分子イメージング施設とGMPバリデーション

GMP Validation for PET Molecular Imaging Facilities in Advanced Molecular Imaging Center (AMIC) at Oita University

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はじめに

近年，PETを用いた分子イメージング技術は，臨床現場での疾患診断に限らず，創薬やバイオマーカーの評価法としても期待されている。大分大学医学部附属先端分子イメージングセンター（AMIC）は，2011年９月より^{18}F-FDGを用いたPET診療を開始している。2012年４月からは，^{11}C-メチオニンを用いた臨床研究を開始した。当施設では，住友重機械製サイクロトロンHM-20S，シーメンス製PET-CT装置を有し，自家製造によるPET薬剤を用いた分子イメージング解析を実施している。幅広いPET薬剤の製造，分子イメージング解析も実施可能であり，PETを利用した「創薬における前臨床試験ならびにマイクロドーズ試験」の実施も可能である。

本施設では，それに伴い必要となる「GMPバリデーション」を計画的に実施し，施設の適格性を証明するため定期的な環境モニタリングを実施している。関連機器類については，設計の検証，据付後の実地検証，性能の実地検証の結果を文書化し，さらに総合的な製造工程の能力評価もあわせて実施している。ソフト面では，PET薬剤の製造管理，品質管理と衛生管理に関する基準書，標準操作手順書（SOP）を作成し，文書管理規程により各文書の体系，書式，運用等を定め，製品標準書の内容や標準操作手順書を理解するために教育訓練を行っている

大分大学医学部附属病院は，「治験中核病院」として認定を受けており，病院内に設置された「総合臨床研究センター」を中心として，臨床研究がスムーズに展開できる病院である。したがって，当病院はPET分子イメージングを利用した治験への応用に十分対応できる施設である。

1．大分大学医学部附属先端分子イメージングセンター（AMIC）の施設概要

大分大学AMICで製造するPET薬剤は，薬事法に対応したGMPレベルで製造することを念頭においており，注射剤の無菌・無麻の基準を満たすように製造しているこれらを満足できるように治験薬GMPハードおよびソフトを構築した。

①ホットラボ室とホットセル

ホットラボ室（図１）では保険診療と臨床研究の両方に対応したPET薬剤の製造が行われている。ホットラボ

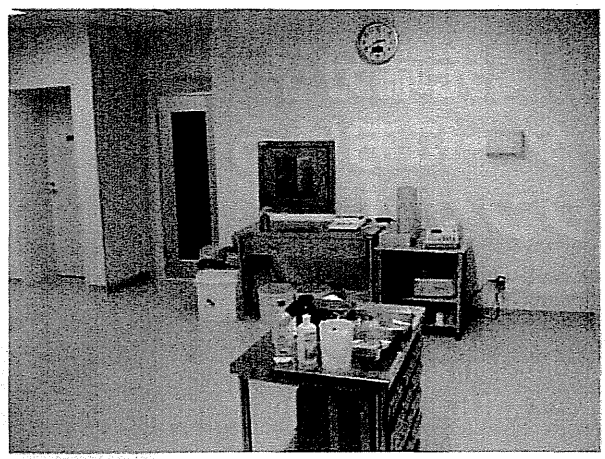

図1　ホットラボ室

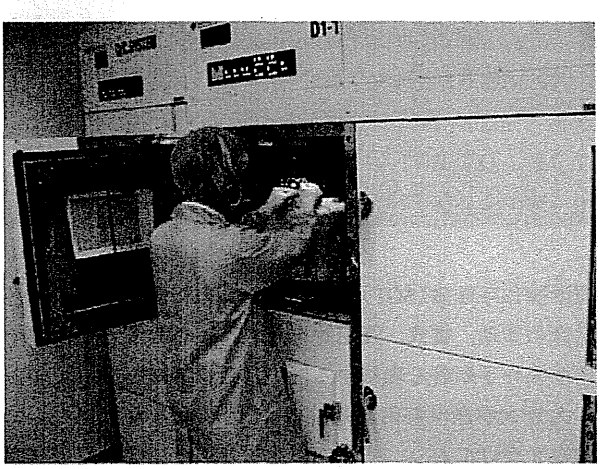

図2　ホットセル内^{18}F-FDG自動合成装置における装着作業

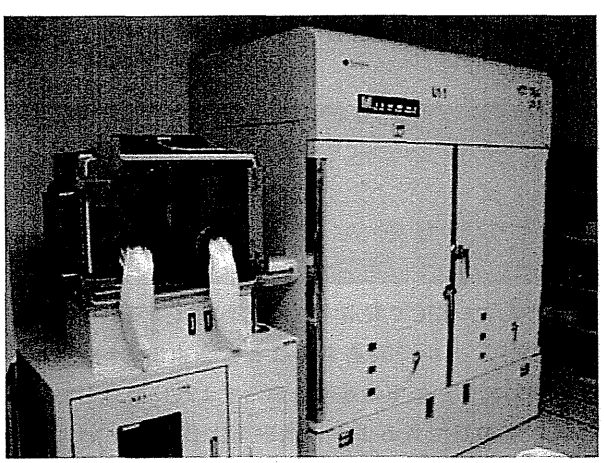

図3　ホットセルに連結された滅菌アイソレーター

室はサイクロトロン室と隣接しており，住友重機械製サイクロトロンHM-20Sで製造された放射性核種(^{18}F，^{11}C)が配管を通してPET薬剤合成装置へ送られる。PET薬剤合成装置は，放射線防護の観点から作業時は密閉されたホットセル内でコンピュータ制御により遠隔操作される。ホットセル内(**図2**)はグレードA(クラス100)の環境であり，ホットセルが置かれているホットラボ室内もグレードB(クラス10,000)に設定することで，クリーンな環境を維持している。ホットセル内は放射線障害防止法に基づくと放射性物質の封じ込め(陰圧)が求められており，一方，無菌・無塵を担保するためには陽圧の環境下を作る必要がある。大分大学AMICに導入された住友重機械製ホットセルは，ホットセル内部にクリーンユニットが設置され，HEPAフィルターを通してクリーンな空気を取り入れることで陽圧を達成している。さらに，内扉と外扉(鉛扉)の間に排気口を設け，内部から漏れ出す放射性物質を排気している。このような工夫により，放射線防護と無菌・無塵の両観点からの基準を満たしている。また，ホットセルの1つはエアレックス社製「滅菌アイソレーター」に接続されている(**図3**)。アイソレーター内はグレードAに設定され，製造されたPET薬剤の充填容器をあらかじめ過酸化水素で滅菌したうえで分注操作を行うことで，高い無菌性を担保している。

②品質管理室と分析室

品質管理室には原料および試薬類の保管庫が設置され，試薬の管理上，各保管庫は5分ごとに測定温度が電子記録されている。さらに液体クロマトグラフィー，ガスクロマトグラフィー，試料保管用のディープフリーザー，およびドラフトが設置されている。品質管理室はホットラボ室と隣接しており，グレードB(クラス10,000)に設定されている。隣接する部屋間または廊下側の壁にはパスボックスを設置しているので，試薬類の搬入，製品の

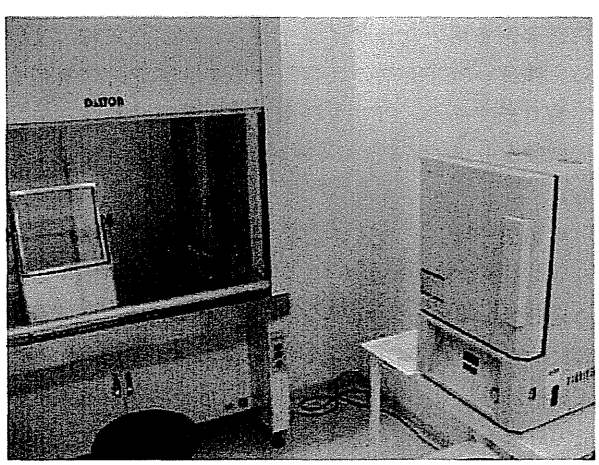

図4　無菌試験用クリーンベンチとインキュベーター

取出し口として活用している。分析室(**図4**)は品質検査室と隣接しており，さらに小部屋(機器室2，検体保管室)が隣接しているので，消耗品や機器類の収納スペースとして活用している。分析室内にはクリーンベンチとインキュベーターが置かれている。分析室では無菌試験を実施している。この部屋もグレードB(クラス10,000)に設定されている。

③作業保管室

作業保管室はホットラボ室と隣接し，パスボックスを通して物品の受け渡しをしている。作業保管室には流し，乾燥機，乾熱滅菌機などの機器類が設置されているので，ホットラボ室から使用済みの器具類を洗浄・滅菌のために受け入れ，滅菌済みの必要物品をホットラボ室へ搬出している。作業保管室には，クリーンベンチとインキュベーターも設置されており，無菌試験の陽性対照菌を使用する際，菌類の持ち込みが分析室内(クラス10,000)へ制限されるため，この部屋で無菌試験を実施できる。グレードC(クラス100,000)に設定されている。

2. GMPバリデーション・クオリフィケーションの実際

このような背景の下，設計の検証として設計時適格性評価(Design Qualification: DQ)，据付後の実地検証としての設備据付時適格性評価(Installation Qualification: IQ)，性能の実地検証としての運転時適格性評価(Operation Qualification: OQ)，PET薬剤の総合的な製造工程の能力評価としての性能適格性評価(Performance Qualification: PQ)の順に実施した。

3. GMPソフトの整備

衛生管理基準書，製造管理基準書，製造体制基準書，品質管理基準書の4本柱で当施設のGMP基準を制定している。「衛生管理基準書」においては，衛生環境を適切に維持管理するための基準について定めている。「製造管理基準書」においては，PET薬剤の製造管理を適切に実施するため，試薬等の保管管理，製造工程の管理等について定めている。「製造体制基準書」においては，PET薬剤の適切な製造管理および品質管理を確保するために必要な体制を定めている。「品質管理基準書」においては，品質管理を適切に実施するため，検体の採取，品質試験方法，試験結果の判定方法等について定めている。

①衛生管理基準

清浄度区分の基本的な考え方として，WHO-GMPにおける無菌操作によって製造される注射剤の製造環境などを参考として設定した。原則としてPET薬剤の製造に関与する作業室を，それぞれの作業内容，品質として要求されるレベルなどによって区分分割し，それぞれの区分ごとに基準をあわせた衛生管理基準を設定している(**図5**)。

また，交叉汚染を起こさないよう，作業員および物品の動線についても制定している。衛生管理上重要となる，定期的清掃，作業員の服装，環境モニタリングなどの衛生環境管理，作業員の教育についてもこの基準書で基本方針が示されている。

②製造体制基準

適切な品質管理の下に被験薬を製造するため，被験薬製造部門と被験薬品質部門を独立させ，それぞれに責任者を任命し，両部門を運用管理者(製造責任者)が統括している。さらに，科学的観点から被験薬を審査するため，

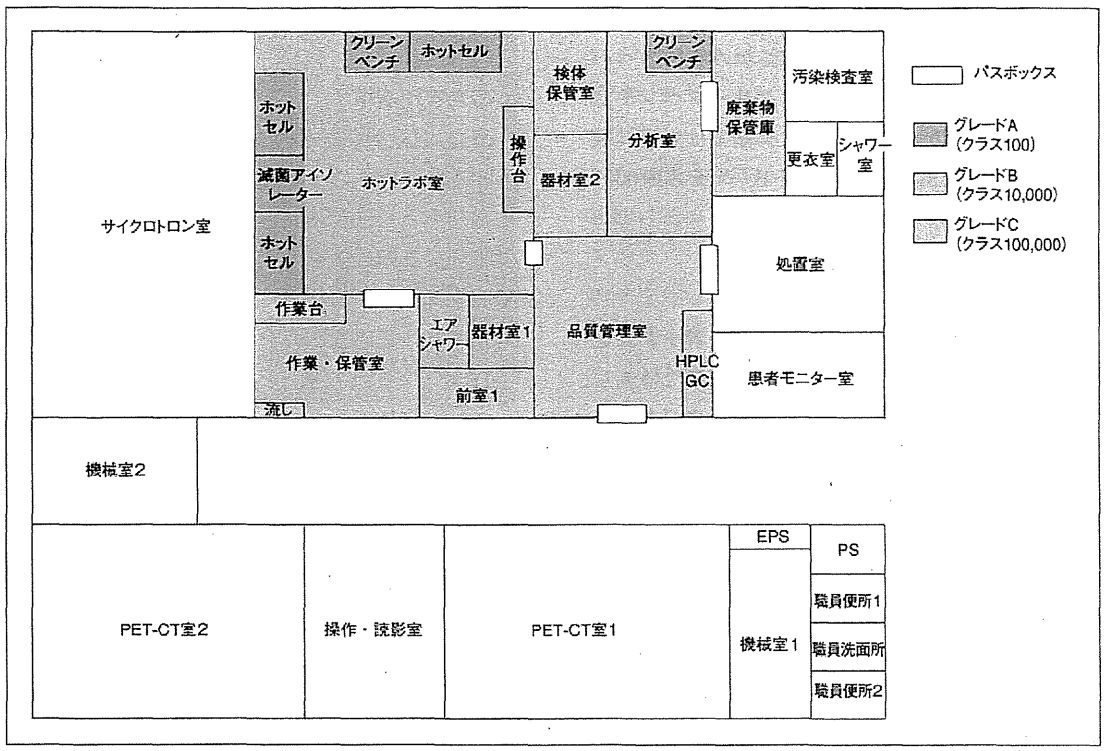

図5　AMICにおける各部屋の清浄度区分

PET-GMP運用委員会を設置している。

③製造管理基準

原料およびPET薬剤の保管管理，PET薬剤の出荷管理，製造工程管理，製造作業における作業管理，無菌を必要とするPET薬剤の製造管理についての基準を定めている。

④品質管理基準

PET薬剤等の検体採取，試験結果の判定および報告，出荷(臨床供給)に関わる総合判定などについての基準が定められている。なお，各PET薬剤における品質検査の項目，基準値等については，「被験薬に関する文書」に記載されている。基準値についてはPET-GMP運用委員会で審議され，承認されている。

4．PET薬剤の製造

各PET薬剤の製造については，「被験薬に関する文書」を作成し，製造方法に関する情報を記載している。使用する試薬については規格・基準を，製造器具類については仕様を定めている。大分大学AMICでは，「被験薬に関する文書」として，^{18}F-FDG，^{11}C-メチオニン，^{11}C-PiBに関する文書の中に製品標準書を記載し，保存している。さらに，製造の各工程におけるチェックを目的とした製造指図書兼製造記録を用意し，製造ロットごとに記載を行っている。これらの文書の内容については，PET-GMP運用委員会においてPET薬剤に関する専門知識を有する委員の下で審議され，適正な製造方法であることが承認されている。作業者は，製品標準書や標準操作手順書の内容に関する教育訓練を受けた後，作業にあたっている。

5．PET薬剤の品質試験

各PET薬剤の品質試験についても，「被験薬に関する文書」に記載されている。^{18}F-FDG，^{11}C-メチオニン，^{11}C-PiBに関する試験方法が記載されている。また，品質試験工程における準備，試験，後片付けなどの標準操作手順書を作成している。品質管理記録を製造ロットごとに記載し，保存している。また，製造工程における準備，製造，後片付け，消毒などの標準操作手順書を作成している。これらの記載内容についても，PET-GMP運用委員会においてPET薬剤に関する専門知識を有する

委員の下で審議され，適正な品質管理方法であることが承認されている。品質試験は，日本薬局方「一般試験法」や放射性医薬品基準「一般試験法」を準用して行っている。また，作業者は，品質基準書や標準操作手順書の内容に関する教育訓練を受けた後，作業にあたっている。

6．製造施設の環境モニタリング

GMPエリア内については，日本薬局方「無菌医薬品製造区域の微生物評価試験法」に準拠した方法で，定期的に環境モニタリングを行っている。グレードAのエリアについては原則週１回，グレードBのエリアについては原則月１回の頻度で測定を行っている。測定項目は，浮遊粒子数，浮遊微生物，付着微生物の３種類であり，これまでのところ良好な結果を得ている。測定結果を監視しながら，随時清浄度の確保に努めている。

7．GMP基準の動向

平成24年２月，厚生労働省からPET・SPECTの放射性医薬品を含む医薬品のGMP査察等に関する新しい通知が公示された。PIC/SのGMPガイドライン活用に関する通知である。Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)とは，医薬品の品質保証・GMP査察の国際連携の組織である。PIC/Sガイドラインをわが国で活用する考え方，品質確保の手法，アネックス１には無菌医薬品の製造，アネックス13には治験薬の製造，特に最近の動きであるPET・SPECTの放射性医薬品のGMP適合性調査の留意点をアネックス３に取りまとめている。PIC/Sは欧州諸国を中心に結成され，昨年１月に米国がようやく加盟した。わが国は平成24年３月９日にPIC/S加盟申請を行ったので，本年中には加盟申請が承認されると期待している。当施設としてもこのようなグローバルなGMP基準に対応していくつもりである。

8．PET分子イメージングを利用した治験への対応

大分大学医学部附属病院は，「治験中核病院」として認定を受けており，病院内に設置された「総合臨床研究センター」を中心として，臨床研究がスムーズに展開できる病院である。また，上述のようにGMP対応施設として提供するPET薬剤の品質は治験にふさわしいものである。したがって，当病院は製薬企業から受託する形でPET分子イメージングを利用した治験に十分対応できる施設である。

まとめ

大分大学医学部附属病院に併設された大分大学AMICは，開設から１年を経ようとしている。保険診療と臨床研究の２本柱での運用は充実している。大分大学AMICは，既存の建屋の改築でできた施設ではなく，新築の施設である。したがって，最新の運用レベルを新設時から取り入れることができた点は，本センターの強みである。製薬企業の方々には，ぜひ見学に来ていただき，新薬開発での利用をご検討いただきたいと思っている。当センターには化学合成，合成装置の開発に詳しい研究者が在籍している。今後，腫瘍検出のPET，受容体占有率の解析に利用できるPET，アミロイドβ解析のPETなど，新薬開発に利用可能なPET薬剤の数を少しずつ増やしていくつもりである。同時に，グローバルな規格に沿ったGMPバリデーションを進めていきたいと考えている。

Age-Specific Sex-Related Differences in Infections: A Statistical Analysis of National Surveillance Data in Japan

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Abstract

Background: To prevent and control infectious diseases, it is important to understand how sex and age influence morbidity rates, but consistent clear descriptions of differences in the reported incidence of infectious diseases in terms of sex and age are sparse.

Methods and Findings: Data from the Japanese surveillance system for infectious diseases from 2000 to 2009 were used in the analysis of seven viral and four bacterial infectious diseases with relatively large impact on the Japanese community. The male-to-female morbidity (MFM) ratios in different age groups were estimated to compare incidence rates of symptomatic reported infection between the sexes at different ages. MFM ratios were >1 for five viral infections out of seven in childhood, i.e. male children were more frequently reported as infected than females with pharyngoconjunctival fever, herpangina, hand-foot-and-mouth disease, mumps, and varicella. More males were also reported to be infected with erythema infectiosum and exanthema subitum, but only in children 1 year of age. By contrast, in adulthood the MFM ratios decreased to <1 for all of the viral infections above except varicella, i.e. adult women were more frequently reported to be infected than men. Sex- and age-related differences in reported morbidity were also documented for bacterial infections. Reported morbidity for enterohemorrhagic *Escherichia coli* infection was higher in adult females and females were reportedly more infected with mycoplasma pneumonia than males in all age groups up to 70 years.

Conclusions: Sex-related differences in reported morbidity for viral and bacterial infections were documented among different age groups. Changes in MFM ratios with age may reflect differences between the sexes in underlying development processes, including those affecting the immune, endocrine, and reproductive systems, or differences in reporting rates.

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Introduction

Manifestation and morbidity of infections differ between the sexes and among different ages. For example, among viral infections, commonly accepted risk factors for enterovirus infections such as herpangina and hand-foot-and-mouth disease (HFMD) include age younger than 1 year and male sex, suggesting a predominance in male infants [1]. Further support for this idea came from a study on HFMD outbreaks in China [2], which demonstrated that boys were more susceptible than girls with the odds ratio of 1.56 (95% confidence interval [95%CI] 1.56–1.57). Although the major bulk of patients with erythema infectiosum (EI) are school-aged children, mothers are more infected than fathers, suggesting a female predominance in adulthood [1]. In addition, more patients with arthropathy, a major complication of EI in adults, are female than male [1,3]. More girls than boys also acquired human herpesvirus (HHV-6), the pathogen of exanthema subitum (ES), in childhood; the acquisition of the virus was associated with female sex with the adjusted hazard ratio of 1.7 (95%CI 1.2–2.4) [4]. By contrast, more males contracted mumps in a large outbreak in Bosnia and Herzegovina in 2010–2011, a pattern which was also seen in the 2010 outbreak of rubella in Bosnia and Herzegovina [5].

With regards to bacterial infections, there was a reported male predominance in the incidence of tuberculosis across all age groups except for 15–24 year olds [6]. In contrast to that, the morbidity of pertussis is slightly higher in adult females [7], and during a recent German outbreak of *Escherichia coli* O104 in 2011, the majority of infected people were adults, and women were infected at about twice the rate as men [8,9].

There are several studies describing age-specific sex-related differences in morbidity. The authors recently demonstrated that

for influenza (H1N1) 2009 and seasonal influenza, the reported morbidity rate for males under twenty years old was statistically higher than that for females, while the relationship was reversed in adulthood [10]. Similar male predominance early in life and reversal at later ages were observed in human T-cell leukemia virus type I (HTLV-I) infection from blood donor data [11]. Thomas and Hall described age-specific sex-related differences in the morbidity of herpes zoster in the US [12], while Wu showed the annual incidence rates of chickenpox by age-group and sex, as well as the relative risks between sexes, using a large-scale database in Taiwan [13].

But studies which describe both age-specific and sex-related differences in morbidity are exceptional; the phenomenon is poorly documented in the literature as a recent review by the authors demonstrated. For example, one study reported that boys were more likely to be infected with adenovirus than girls, but no age-specific incidences were given by sex [14]. Reports by Zerr et al. [4] and Hukic et al. [5] described differences in morbidity for HHV-6 and mumps infections between the sexes, but did not mention age-specificity at all. In an analysis of serological surveys of the age-specific distribution of antibody to parvovirus B19, the pathogen of EI, no sex-related difference was described [15]. No sex-related age-specific difference in morbidity was mentioned in a survey on mumps in US [16]. Tan reported a thorough review on pertussis with international burden, but no description was given regarding sex-related difference in morbidity [17]. In a review on morbidity and mortality for vaccine-preventable diseases in the US, no description was given of sex-related differences in morbidity and mortality [18].

Even in a standard textbook of pediatrics [1] or handbook of communicable diseases [7], many infectious diseases are described with no information given about age-specific sex-related differences in their epidemiological profiles. Although peak ages of incidence or prevalence are detailed for many diseases, there is rarely any description of sex-based differences, including when such difference by sex occurs, until what age it continues, and what mechanism(s) might account for this effect. These shortcomings in knowledge can potentially hinder our understanding and control of infectious diseases.

The authors have developed a mathematical model based on nationwide data which enables the comparison of symptomatic reported morbidity rates of males and females by age groups [10]. The aim of the present study is to describe age-specific sex-related differences in infections using the Japanese nationwide infectious disease database and to consider sex- and age-related differences in viral and bacterial infections.

Methods

Ethics statement

Ethical approval and signed patient consent forms were not required for our study according to the Guideline for Epidemiological Studies [19], which was established by the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science and Technology of Japan in accordance with the World Medical Association's Declaration of Helsinki and Japan's Act on the Protection of Personal Information and other related acts. Specifically, (1) all individual data were collected by law and authorized to be utilized for academic purposes [20], and (2) patients could not be identified, as all data were de-identified; i.e., stripped of personal identifiers.

Study population and data sources

Japan has an active infectious disease surveillance system. Since 1999, the National Institute of Infectious Disease (NIID; Tokyo, Japan) has collected reports of patients with various infectious diseases, and the data have been reported in sex and age groups (National Epidemiological Surveillance of Infectious Diseases, NESID) [21]. Diseases of interest in the present study were selected from those reported in NESID.

Viral infectious diseases without availability of vaccination reported from the pediatric sentinel points. Five major viral diseases are reported from the pediatric sentinel points of NESID: pharyngoconjunctival fever (PCF), herpangina, hand-foot-and-mouth disease (HFMD), EI, and ES. No vaccinations are available for these diseases in Japan. Data were collected from approximately 3000 pediatric sentinel points all over Japan between 2000 and 2009 (Table 1). The number of the sentinel points represents approximately 10% of the pediatric facilities in Japan, and the average number of sentinel points in 2009 was 3,022. As shown in Table 1, the numbers of male and female cases from the sentinel points were reported across 13 age groups, and adult cases were also reported.

Vaccine-preventable viral infectious diseases reported from the pediatric sentinel points. Two vaccine-preventable viral infectious diseases, mumps and varicella, were studied using reports from the pediatric sentinel points of NESID. Vaccinations for mumps and varicella are optional for children older than 1 year under the Japanese law with vaccination rates being 23.2% and 21.3% against mumps and varicella, respectively [22]. The vaccination rates for those two infections are only available for combined males and females - vaccination rates for males and females were not available separately. However, it is assumed that there are no differences in the vaccination rates between the sexes, based on data from vaccination rates for the measles-rubella combination vaccine in Japan where rates are available for each sex, and there is no difference in the vaccination rates between the sexes [10,23].

Bacterial infectious diseases. Data for four bacterial infections were available from NESID for the present study (Table 2); Group A streptococcal pharyngitis (GAS), pertussis, enterohemorrhagic *Escherichia coli* (EHEC), and Mycoplasma pneumonia (MP). GAS and pertussis were reported from the pediatric sentinel points. EHEC cases must, by law, be reported by all clinical facilities in Japan and archived in NESID, while the data for MP were collected from approximately 470 NESID sentinel points. Of these, only pertussis is vaccine-preventable; the vaccine is generally provided four times between 3 months and 7·5 years as a component of the diphtheria, tetanus and pertussis combined vaccine which is recommended under Japanese law with a vaccination rate of 95.8% [22].

Statistical model and data analysis

Male-to-female morbidity ratios of infectious diseases without vaccine availability. Morbidities of males and females in each age group were compared through the male-to-female morbidity (MFM) ratios [10], statistics similar to ones used by Green [24] and Reller et al [25]. Since the present sampling is based on the data reported from the sentinel points, the sampling is viewed as a Poisson sampling. The morbidities (symptomatic incidence) at a current time, p_M and p_F, cannot be estimated from the observational patient data. Let π_M and π_F be the probabilities that male and female patients in the age group visit the sentinel points, respectively. From the present sampling from the sentinel points, the ratio $\gamma = \frac{\pi_M p_M}{\pi_F p_F}$ can be estimated by maximum

Table 1. Numbers of cases and male-to-female morbidity ratios of viral infections reported from the pediatric sentinel points from 2000 to 2009 in Japan.

		Age	0	1	2	3	4	5	6	7	8	9	10–14	15–19	≥20
Infection without vaccination available	Pharyngo-conjunctival fever	Male	12767	42019	35164	39772	38487	30997	18169	10849	7224	4736	7718	674	2710
		Female	9828	31158	28769	32303	32039	25289	15768	9704	6495	4205	6290	623	6159
		M/F (95%CI)	1.23 (1.19–1.28)	1.28 (1.25–1.31	1.16 (1.14–1.19)	1.17 (1.15–1.20)	1.14 (1.11–1.16)	1.17 (1.14–1.20)	1.10 (1.06–1.13)	1.06 (1.02–1.11)	1.06 (1.01–1.11)	1.07 (1.01–1.14)	1.17 (1.11–1.23)	1.03 (0.88–1.21)	0.47 (0.44–0.50)
	herpangina	Male	59707	156797	124871	102487	78634	52619	26410	14268	8337	5118	7668	943	2378
		Female	50588	136847	116722	95002	74895	48590	25267	14051	8228	5196	6677	925	4751
		M/F (95%CI)	1.12 (1.10–1.14	1.09 (1.08–1.10)	1.02 (1.01–1.03)	1.03 (1.01–1.04)	1.00 (0.99–1.01)	1.03 (1.01–1.05)	0.99 (0.97–1.02)	0.97 (0.93–1.00)	0.96 (0.92–1.01)	0.94 (0.89–0.99)	1.09 (1.04–1.15)	0.97 (0.85–1.11)	0.54 (0.50–0.58)
	hand-foot-and-mouth disease	Male	36820	148707	132150	108946	87667	61360	30191	15216	9401	5635	8159	528	2025
		Female	30282	118713	109409	88077	72002	48905	25046	13271	8256	5076	7319	678	7496
		M/F (95%CI)	1.15 (1.13–1.18)	1.19 (1.18–1.20)	1.15 (1.14–1.16)	1.18 (1.16–1.19)	1.16 (1.14–1.18)	1.19 (1.17–1.22)	1.15 (1.12–1.18)	1.09 (1.05–1.13)	1.08 (1.04–1.13)	1.06 (0.999–1.11)	1.06 (1.01–1.11)	0.74 (0.63–0.88)	0.29 (0.27–0.31)
	erythema infectiosum	Male	8592	12927	14981	24210	33013	36941	29507	23196	16828	11233	14160	286	1152
		Female	8308	11159	13856	22502	32320	35788	30213	24800	18581	12220	13923	729	8287
		M/F (95%CI)	0.98 (0.94–1.03)	1.10 (1.06–1.14)	1.03 (0.99–1.06)	1.02 (0.998–1.05)	0.97 (0.95–0.995)	0.98 (0.96–1.004)	0.93 (0.91–0.95)	0.89 (0.87–0.91)	0.86 (0.84–0.89)	0.87 (0.84–0.91)	0.97 (0.94–1.002)	0.37 (0.30–0.46)	0.15 (0.14–0.16)
	exanthema subitum	Male	373434	179507	13653	1909	658	436	342	291	209	157	199	30	58
		Female	358470	164154	12857	1837	601	378	309	224	207	130	158	14	116
		M/F (95%CI)	0.99 (0.98–1.00)	1.04 (1.03–1.05)	1.01 (0.98–1.05)	0.99 (0.90–1.09)	1.04 (0.89–1.23)	1.10 (0.90–1.35)	1.05 (0.84–1.32)	1.24 (0.96–1.60)	0.96 (0.72–1.28)	1.15 (0.82–1.62)	1.20 (0.88–1.63)	2.04 (0.80–5.19	0.54 (0.34–0.85)
Infection with vaccination available	mumps	Male	4594	36580	69515	108637	137520	130210	92099	60145	37935	24507	40165	3353	8123
		Female	3293	27218	57281	91629	118793	109838	79821	53468	34277	21889	35995	3952	16112
		M/F (95%CI)	1.32 (1.24–1.42)	1.28 (1.25–1.31)	1.15 (1.14–1.17)	1.13 (1.11–1.14)	1.10 (1.09–1.12)	1.13 (1.12–1.14)	1.10 (1.08–1.11)	1.07 (1.05–1.09)	1.05 (1.03–1.08)	1.07 (1.04–1.09)	1.06 (1.04–1.08)	0.81 (0.75–0.86)	0.54 (0.52–0.56)
	varicella	Male	109643	241632	234577	225454	196204	131974	66813	32708	19237	11455	18494	2108	7036
		Female	104740	218016	216904	204682	179400	117473	61408	30851	18679	11308	17515	1918	7222
		M/F (95%CI)	0.99 (0.98–1.01)	1.05 (1.04–1.06)	1.03 (1.02–1.04)	1.05 (1.04–1.06)	1.04 (1.03–1.05)	1.07 (1.06–1.08)	1.03 (1.02–1.05)	1.01 (0.99–1.03)	0.98 (0.95–1.01)	0.96 (0.93–1.001)	1.00 (0.97–1.04)	1.05 (0.95–1.14)	1.05 (0.996–1.10)
Male-to-female population ratio (2000–2009)			1.053	1.052	1.051	1.50	1.50	1.50	1.051	1.051	1.051	1.051	1.051	1.052	1.042

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Table 2. Numbers of cases and male-to-female morbidity ratios of bacterial infections reported from the sentinel points from 2000 to 2009 in Japan.

	Age	0	1	2	3	4	5	6	7	8	9	10–14	15–19	≥20
group A streptococcal pharyngitis	Male	6932	30523	57869	111793	171059	191417	156717	113858	80190	54206	92088	7300	1101947
	Female	5865	24300	46038	85565	133386		147536	101195	74156	51505	80950	7361	954360
	M/F (95%CI)	1.12 (1.07–1.18)	1.19 (1.16–1.22)	1.20 (1.17–1.22)	1.24 (1.23–1.26)	1.22 (1.21–1.23)		1.14 (1.13–1.16)	1.07 (1.06–1.08)	1.03 (1.01–1.04)	1.00 (0.98–1.02)	1.08 (1.07–1.10)	0.94 (0.90–0.99)	0.45 (0.45–0.46)
pertussis	Male	4095	1505	654	683	578	501	357	356	366	382	1239	280	13080
	Female	3737	1384	750	733	683	468	399	347	361	343	1380	376	15430
	M/F (95%CI)	1.04 (0.97–1.11)	1.03 (0.93–1.15)	0.83 (0.71–0.97)	0.89 (0.76–1.03)	0.81 (0.68–0.95)	1.02 (0.85–1.23)	0.85 (0.69–1.05)	0.98 (0.78–1.21)	0.96 (0.78–1.20)	1.06 (0.85–1.31)	0.85 (0.76–0.96)	0.71 (0.56–0.89)	0.50 (0.46–0.54)
Male-to-female population ratio*		1.053	1.052	1.051	1.050	1.050	1.050	1.051	1.051	1.051	1.051	1.051	1.052	1.042

	Age	0	1–4	5–9	10–14	15–19	20–29	30–39	40–49	50–59	60–69	70≤
enterohemorrhagic *Escherichia coli*	Male	339	5344	3309	1645	1355	2698	1672	937	904	778	728
	Female	278	4344	2657	1280	1280	3064	2232	1299	1699	1122	1345
	M/F (95%CI)	1.16 (0.92–1.46)	1.17 (1.10–1.24)	1.19 (1.10–1.28)	1.22 (1.10–1.36)	1.01 (0.90–1.13)	0.85 (0.78–0.91)	0.73 (0.67–0.81)	0.71 (0.63–0.81)	0.54 (0.48–0.61)	0.75 (0.65–0.86)	0.81 (0.71–0.92)
mycoplasma pneumonia	Male	624	12013	9691	4358	731	784	720	347	273	354	813
	Female	836	13244	10170	4782	968	1842	1760	649	525	451	755
	M/F (95%CI)	0.71 (0.64–0.79)	0.86 (0.84–0.88)	0.91 (0.88–0.93)	0.87 (0.83–0.90)	0.72 (0.65–0.79)	0.41 (0.38–0.44)	0.40 (0.37–0.44)	0.53 (0.46–0.60)	0.53 (0.46–0.61)	0.85 (0.74–0.97)	1.60 (1.45–1.77)
Male-to-female population ratio		1.053	1.051	1.051	1.051	1.052	1.042	1.022	1.010	0.985	0.928	0.671

*identical to the bottom row of the Table 1.

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likelihood estimator $\hat{\gamma}=\frac{n_M/N_M}{n_F/N_F}=\frac{n_M}{n_F}\frac{N_F}{N_M}$, where N_M and N_F are the subpopulations of males and females in an age group in Japanese population; i.e. fixed values, and n_M, and n_F are the random variables that describe the numbers of male and female patients. The ratio is referred to as the apparent MFM ratio. If $\frac{\pi_M}{\pi_F}=1$, then, $\gamma=\frac{p_M}{p_F}$ is the true MFM ratio. For large n_M and n_F, $\log\hat{\gamma}$ is asymptotically normally distributed with mean $\log\gamma$ and variance $\frac{1}{n_M}+\frac{1}{n_F}$. In order to make multiple tests of MFM ratios in age groups, the Bonferroni method [26] is employed, and the Bonferroni 95% joint confidence intervals of MFM ratios are constructed.

In order to estimate MFM ratios, ratios of male and female population sizes in age groups should be paid attention, as explained above. The male-to-female population ratios in age were almost constant from 2000 to 2009. Ratios of average subpopulations of males and females from 2000 to 2009 were used in this study (Table 1).

Male-to-female morbidity ratios of vaccine-preventable pediatric infectious diseases. Let ω_{vM} and ω_{vF} be the probabilities that male and female patients in the age group get vaccinated and let ω_{iM} and ω_{iF} be the probabilities that vaccinated male and female patients in the age group get immunized, respectively. From the present sampling from sentinel points, the ratio $\gamma=\frac{(1-\omega_{vM}\omega_{iM})\pi_M p_M}{(1-\omega_{vF}\omega_{iF})\pi_F p_F}$ can be estimated by maximum likelihood estimator $\hat{\gamma}=\frac{n_M/N_M}{n_F/N_F}=\frac{n_M}{n_F}\frac{N_F}{N_M}$. If $\frac{\omega_{vM}}{\omega_{vF}}=\frac{\omega_{iM}}{\omega_{iF}}=1$ and $\frac{\pi_M}{\pi_F}=1$, then, $\gamma=\frac{p_M}{p_F}$ is the true MFM ratio.

Results

MFM ratios of viral infections

Viral infectious diseases without availability of vaccine. MFM ratios of five viral infectious diseases from NESID for which vaccination is not available are shown in Figure 1A–E. In this study, "children" refers to those aged younger than 15 years of age; "adolescence" 15–19 years of age and "adult" 20 years of age. In two diseases, MFM ratios of children under 15 years old were >1, i.e. male children under 15 years old were significantly more likely to be reported as infected with PCF, and HFMD ($p<0.05$, Figure 1A, C). The MFM ratios for reported cases of herpangina were >1 in 0–3, 5 and 10–14 years old ($p<0.05$, Figure 1B). The MFM ratios for reported EI was >1 only in children 1 year of age (MFM ratio 1.10, 95% confidence interval [95%CI] 1.06–1.14; Figure 1D). Of interest, MFM ratios for the above four diseases decreased to <1 by adulthood; i.e., by adolescence (15–19 years old), females were more frequently reported to be infected than males with HFMD (MFM ratio 0.74, 95%CI 0.63–0.88; Figure 1C), and by adulthood (≥20 year old) women were more affected than men by PCF (MFM ratio 0.47, 95%CI 0.44–0.50; Figure 1A) and herpangina (MFM ratio 0.54, 95%CI 0.50–0.58; Figure 1B). For EI, MFM ratios were <1 in 4, 6–9, and older than 15 years for age (Figure 1D). The MFM ratios for ES were 0.99 (95%CI 0.98–1.00) in 0 year and 1.04 (95%CI 1.03–1.05) in 1 year. In age groups over 4 years of age, the number of cases reported as "ES" were unreliable because ES is clinically unlikely in this group [1,7]. Thus the data are not plotted in age groups ≥ 4 years of age in Figure 1E.

Vaccine-preventable viral infectious diseases. MFM ratios for reported cases of mumps were >1 from 0 to 14 years of age ($p<0.05$) and <1 thereafter (MFM ratio 0.82, 95%CI 0.76–0.87 in 15–19 years of age, Figure 1F). For reported cases of varicella, MFM ratios were >1 in 1–6 year old ($p<0.05$) and not different from 1 in newborns and those older than 7 years (Figure 1G).

MFM ratios of bacterial infections

MFM ratios for reported cases of GAS were >1 in children under 15 years old (except 9 year olds) and <1 after adolescence (≥15 years of age, $p<0.05$); i.e. male children were reported significantly more often as infected than girls, but by adolescence, females were more frequently reported to be infected with GAS than males (MFM ratio 0.93, 95%CI 0.89–0.98 in 15–19 years of age; Figure 2A). In pertussis, the MFM ratios were <1 for children 2 years old, 4 years old, and over 10 years old ($p<0.05$, Figure 2B).

MFM ratios for EHEC were statistically >1 in 1–14 years old ($p<0.05$) and <1 in ages older than 15 years (MFM ratio 0.85, 95%CI 0.76–0.96 in 15–19 years of age; Figure 2C); i.e. boys under 14 years old were more frequently reported to be infected with EHEC than girls, whereas adult females were more reported to be infected with EHEC than males. The age category from 1 to 4 years old had the highest number of reported cases (Table 2).

As shown in Figure 2D, females are statistically more likely to be reported as infected with MP than males, except in elderly people above 70 years old. MFM ratios were the smallest in the age category from 30 to 39 years old (MFM ratio 0.40, 95%CI 0.37–0.44), while the highest number of reported cases is in those aged 1 to 4 years old (Table 2).

Discussion

Viral infections

The present study used the data of NESID, the national surveillance data of Japan, to demonstrate differences by sex and age in the symptomatic incidence of selected viral infections. The estimated incidence rates in Japan are as follows; PCF 22.2 per 1,000 population aged 0–14 years (95%CI 18.4–26.0), herpangina 51.7 (95%CI 47.8–55.6), HFMD 36.7 (95%CI 34.1–39.3), EI 15.2 (95%CI 13.9–16.6), ES 38.5 (95%CI 36.0–41.0), mumps 73.0 (95%CI 68.5–77.6), varicella 86.1 (95%CI 81.8–90.4) [27]. Statistical analysis of seven viral infectious diseases documented that male children are more likely to be reported as symptomatically infected than females in five out of the seven diseases (Figure 1A–C, F–G). Of these five diseases, the MFM ratios decrease to <1 by adulthood for PCF and herpangina, while those for HFMD and mumps were reversed to <1 in adolescence. For EI, the MFM ratio was 1.10 (95%CI 1.06–1.14) at 1 year of age, and ratios were <1 thereafter with smaller ratios ≥15 years of age. This might imply that there are age-specific sex-related differences in the immune response to viruses between childhood and adolescence/adulthood. However, every rule has its exception, and in this case the MFM ratio of varicella did not reverse to <1 in adults. MFM ratio for ES were <1 in infants and >1 at 1 year of age ($p<0.05$).

It is possible that the observed pattern is due to differences in social roles between the sexes; e.g. women may be more likely to take care of sick family members and thus are more likely to be affected by the disease [28]. Information about these diseases was obtained from ~3,000 pediatric sentinel points; adult cases were also reported, probably because some accompanying parents might have consulted the pediatricians about their own health during their children's visit. Hence, there is a possibility that

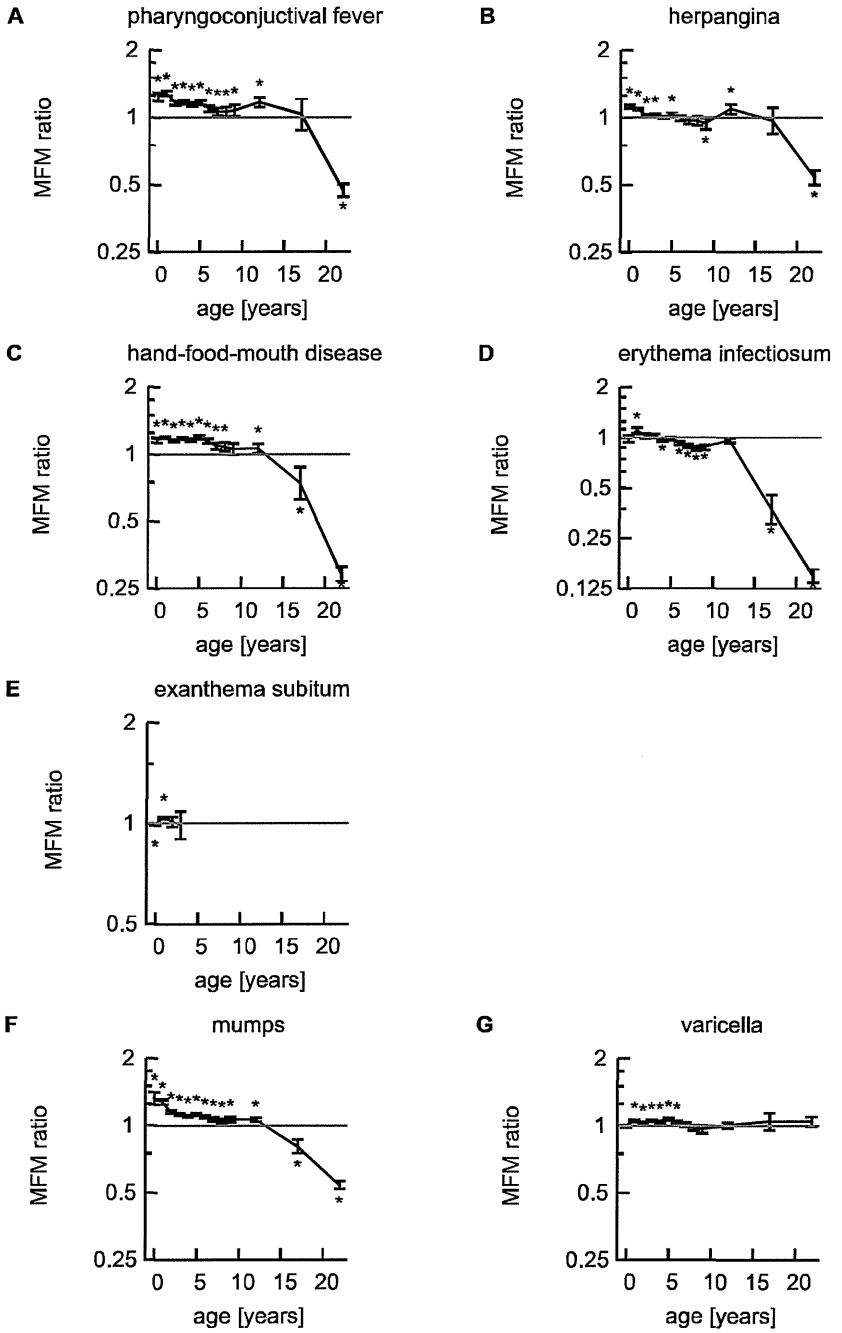

Figure 1. MFM ratios of viral infectious diseases reported from the pediatric sentinel points in Japan; pharyngoconjunctival fever (A), herpangina (B), hand-foot-mouth disease (C), erythema infectiosum (D) and exanthema subitum (E) for infections without availability of vaccination, and mumps (F) and varicella (G) for vaccine-preventable infections in Japan. 95% confidence intervals for MFM ratios are indicated by error bars. Red solid lines indicate MFM ratio of 1. *: Significant with the Bonferroni's correction ($p<0.05/13$) [26].
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reported data for adults might have been gender-biased as it is more likely in Japan that mothers would be the accompanying parent. However, considering that MFM ratio was not different from 1 for varicella in adults (Figure 1G) and that the decreases of MFM ratios of some other diseases were observed from adolescence onwards (≥15 years of age; Figure 1C, D, and F), it is unlikely that the reversal of the MFM ratios was simply due to over-reporting by mothers from the pediatric sentinel points.

Further evidence to the contrary comes from epidemic kerato-conjunctivitis (EKC). The reported numbers of patients with EKC from the ophthalmological sentinel points of NESID (per 100,000) had two peaks at ages 1–4 and 30–39 years of age (Figure 3A), which may imply household transmission. However, MFM ratio was >1 (MFM ratio 1.12, 95%CI 1.11–1.14) in the age group 30–39 years old (Figure 3B), indicating that a bias due to accompanying parent gender would be unlikely.

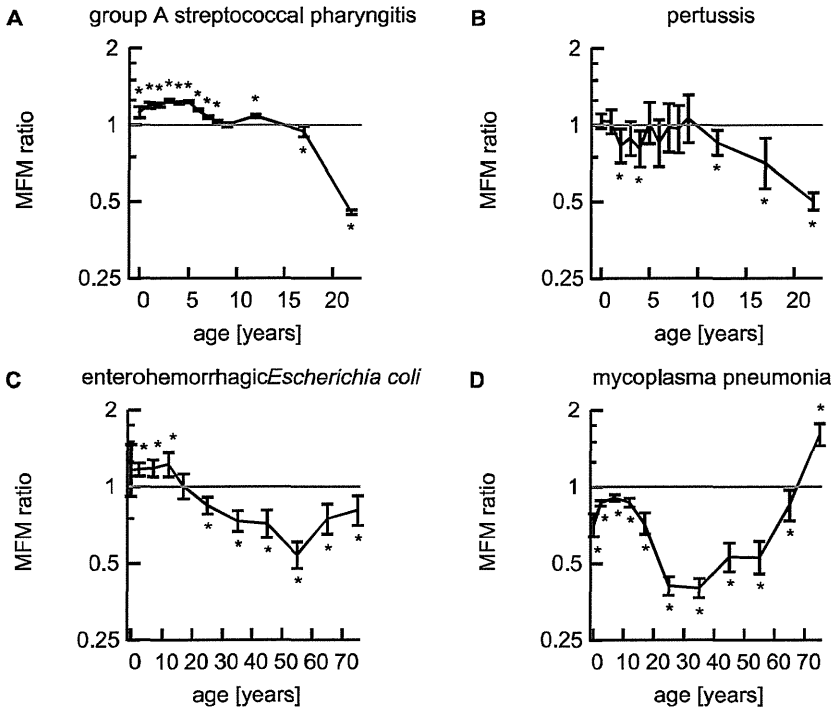

Figure 2. MFM ratios of bacterial infections; group A streptococcal pharyngitis (A), pertussis (B), enterohemorrhagic *Escherichia coli* (C) and mycoplasma pneumonia (D) reported from the sentinel points in Japan. 95% confidence intervals for MFM ratios are indicated by error bars. Horizontal red solid lines indicate MFM ratio of 1. *: Significant with the Bonferroni's correction ($p<0.05/13$ in A and B; $p<0.05/11$ in C and D) [26].
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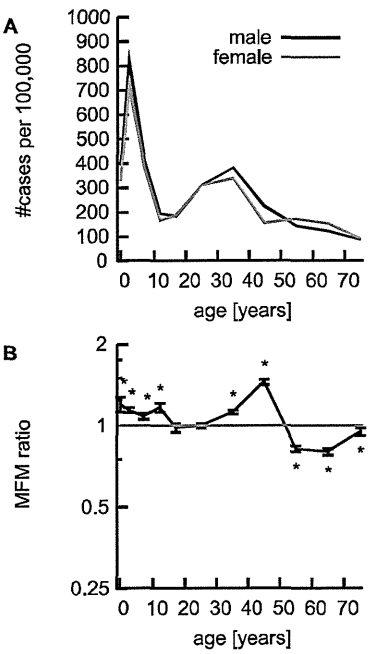

Figure 3. Epidemic keratoconjunctivitis (EKC) reported from the ophthalmological sentinel points in Japan. A: The number of reported cases of EKC (per 100,000 population) are illustrated for male (black) and female (red) separately. B: MFM ratios of EKC. 95% confidence intervals for MFM ratios are indicated by error bars, and horizontal red solid lines indicate MFM ratio of 1. *: Significant with the Bonferroni's correction ($p<0.05/11$) [26].
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Bacterial infections

GAS with an estimated incidence of 66.6 per 1,000 (95%CI 60.5–72.6) [27] showed male predominance in childhood and the reversal in adolescence and adulthood. Morbidity of pertussis was never >1 in children or adults, indicating a female predominance at all ages as described elsewhere [7]. MFM ratios for EHEC were >1 in age groups 1–14 years of age and reversed to <1 in 15 year olds and older, i.e. boys were more likely to be reported as infected with EHEC than girls in childhood, while in adulthood, women were more likely to be reported as infected with EHEC than men. Total numbers of female and male cases with EHEC were 20,600 and 19,709, respectively, including 10,761 female and 7,717 male adult (≥20 years of age) cases (Table 2). Adults comprised 46% of the total cases, and 61% of the adult cases were in females. This is in accordance with the female adult preponderance in the 2011 outbreak of *Escherichia coli* O104 in Germany, where 87% of cases were adults and 68% of those adults were female [9].

Mycoplasma pneumoniae is the pathogen of MP with the second largest incidence rate of community-acquired pneumonia [29]. MP is unique among the bacterial infections examined in this study in that it showed a female preponderance in symptomatic infection at all ages except those over 70 years old (Figure 2D). In a population-based study on incidence of community-acquired pneumonia, it was reported that the incidence for *Mycoplasma pneumoniae* infection was not different in young and elderly people, and it was identical in males and females [29]. But the population size surveyed was ~200,000 and it is possible that the test power was not sufficient.

Strengths and weaknesses of the study

Several limitations of the present study should be noted. In general, observational studies do not verify the causality, because exposures to pathogens cannot be controlled. Covariates such as sex and age are confounded by human behavior, cultural influences, and other factors. The data used in the present study has a very large sample size collected through the official nationwide surveillance system in Japan [21]. Conservative 95% Bonferroni joint confidence intervals [26] of MFM ratios (Figures 1, 2 and 3) and assured precision of the estimates made it possible to demonstrate sex- and age-related differences in reported symptomatic infections.

It is possible that reporting rates are influenced by age and sex. In the model of the present analysis, the authors postulate that male and female patients consult physicians at the same rate. We further assume that parents seek health care equally for their sons and daughters. The latter assumption was based on the similar levels of immunization rates for boys and girls [23]. In 2008, male to female immunization ratios of measles-rubella combination vaccine were virtually 1 in children, indicating equality in vaccination rate [10,23]. Identical medical care-seeking was reported in both sexes for salmonellosis in US [25]. Thus, we suggest a sex-based bias in the probability of seeking medical care during childhood is unlikely [10]. The authors believe that any bias in estimates of the MFM ratios introduced by age- and/or sex-based difference in reporting is minimal.

Accurate and precise estimate of morbidity rates depends on complete observation on the number of cases. Incomplete reporting of the number of infected individuals makes it difficult to accurately estimate morbidity rates [30]. The present study analyzed only data of symptomatic cases. The omission of asymptomatic cases might lead to biased results between males and females; it would also be possible that symptomatic to asymptomatic infection ratios differ by sex and age. In this study, the morbidities P_M and P_F are considered to be products of probability of transmission and probability of developing symptomatic disease, neither of which can be estimated separately.

The pathogens of the analyzed infections include both viruses and bacteria. Immunological responses against viruses and bacteria are different. It is therefore worth separately documenting sex- and age-related differences in the reported morbidity of viral and bacterial infectious diseases in order to understand differences in their respective immune responses.

Putting research into context

This study documented examples of age-specific sex- related differences in morbidity for common infections. It also suggested a hypothesis that male children may be more susceptible to many of the common infectious diseases than female children, while this relationship is reversed by adulthood.

An apparent increased susceptibility of male children to selected infectious diseases has been frequently described [24]. But, with the exception of a limited number of studies [10–13], this increased susceptibility has been infrequently described in terms of sex and age as in the present study. In fact, some studies report no differences by sex for some diseases [15–18], for which significant differences were observed in this study. The merit of the methodology of the present study [10] is to show differences in morbidity by sex and age using observational data.

Genetic explanation for male-preponderance of infection in children has been proposed [31,32]. As children grow, their body systems develop, including immune, endocrine and reproductive systems. Both innate and acquired immunity are influenced by reproductive hormones [33–39]. Changes in MFM ratios by age might reflect differences in the relative physiological development of immune, endocrine, and reproductive systems between male and female children as they grow.

Male-to-female differences in response to vaccination (including non-targeted effects) were reported from epidemiological cohort data [40–45], appreciating that the sex differences in immune responses could lead to more efficient vaccination programs [46,47]. Despite data supporting an effect of sex in the response to vaccines, most studies do not document age-specific effects in vaccine efficacy or induced immune responses [47]. It is vital to understand sex- and age-related differences in the morbidity of infectious diseases in order to more efficiently prepare for and control outbreaks, investigate immune responses, and optimize disease-specific vaccine programs [47].

Population-based serological surveys studying antibodies (IgM and IgG) against pathogens or detecting pathogen DNA by polymerase chain reaction [4] would be more ideal in estimating accurate and precise infection rate. However, the cost of such investigations could pose a limiting factor in conducting a study using these methods. Another approach would be a large database where all cases of selected infections in a population are obligated to register, but the possibility of incomplete reporting (deliberate or unintentional) would still exist. The present study analyzed the data of NESID [21]. The sentinel points represent about 10% of all medical facilities in Japan, and the number of sentinel points in public health center areas are approximately proportional to their population size. Since reporting from the sentinel points is mandatory, the authors speculate that data from the sentinel points would proportionately represent the nation-wide trends.

In summary, this study provides evidence through the analysis of national data and calculation of MFM ratios that morbidity for viral and bacterial infections are sex- and age-dependent. Since our method uses observational data, we cannot avoid the possibility of under reporting which might confound the results [30]. However, under the proper circumstances, the methodology presented here may provide a powerful tool to study age-specific sex-related differences in the reported morbidities of selected diseases. These considerations have been poorly documented previously but have lately attracted more attention [48].

Author Contributions

Conceived and designed the experiments: NE OT SH. Analyzed the data: NE OT SH. Contributed reagents/materials/analysis tools: NE SH. Wrote the paper: NE OT KB S. Korematsu. Interpretation of the findings and the statistical assessment: NE OT KB S. Korematsu S. Karukaya KU NO TM.

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